

The opinion in support of the decision being entered today
is *not* binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte DIPAK K. BANERJEE and JUAN A. MARTINEZ

Appeal 2007-1614
Application 09/779,447
Technology Center 1600

Decided: August 14, 2007

Before DONALD E. ADAMS, ERIC GRIMES, and LORA M. GREEN,
Administrative Patent Judges.

GRIMES, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to inhibiting angiogenesis by administering tunicamycin. The Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

BACKGROUND

“Angiogenesis involves the development of new and small blood vessels by budding and sprouting from larger, extant vessels . . .”

(Specification 1). Abnormal or uncontrolled angiogenesis features prominently in a number of diseases (*id.* at 2). Tumor growth, for example, depends on angiogenesis (*id.*). Thus, “[i]n breast carcinoma, intratumoral endothelial cells proliferate 45 times faster than endothelial cells in adjacent benign stroma, and the rate of tumor progression correlates with increased intratumoral microvascular density. Neovascularization supports tumor growth by allowing ‘perfusion’ of nutrients, oxygen, and waste products through a crowded cell population” (*id.*).

The Specification discloses that tunicamycin reduces endothelial cell proliferation in cell culture, with 70% of the cells entering “into apoptosis (i.e., ‘programmed cell death’) after an exposure to [1 µg/ml] tunicamycin for 32 hours” (*id.* at 56). The Specification discloses methods of inhibiting angiogenesis by administering nucleosides, including tunicamycin, “to a patient in need of such treatment, e.g., a patient having disease state characterized by an abnormally high amount of angiogenesis. For instance, the present invention may inhibit neovascularization of a solid tumor tissue” (*id.* at 37).

DISCUSSION

1. CLAIMS

Claims 9, 14, and 18 are pending and on appeal. Claim 9 is representative and reads as follows:

Claim 9: A method for inhibiting angiogenesis, comprising:
administering a nucleoside in an amount effective to
inhibit angiogenesis, to a patient in need of such treatment, the
nucleoside comprising glucosamine, and wherein the
glucosamine comprises at least one tunicamycin and functional
derivatives thereof, and wherein the at least one of tunicamycin

and factional [sic] derivatives thereof is administered for a period of time, subsequently the administration of the at least one of tunicamycin and functional derivatives thereof is suspended for a period of time of at least about 1 week, and subsequently the administration of the at least one of tunicamycin and functional derivatives thereof is resumed.

Thus, claim 9 is directed to a method of inhibiting angiogenesis, in a patient in need of such treatment, by administering tunicamycin or a functional derivative, suspending the treatment for at least one week, and subsequently resuming the treatment.

2. PRIOR ART

The Examiner relies on the following references:

Dipak K. Banerjee et al., *Is asparagine-linked protein glycosylation an obligatory requirement for angiogenesis?*, 30 Indian Journal of Biochemistry and Biophysics 389-394 (December 1993).

Tony Tiganis et al., *Functional and Morphological Changes Induced by Tunicamycin in Dividing and Confluent Endothelial Cells*, 198 Experimental Cell Research 191-200 (1992).

3. OBVIOUSNESS

Claims 9, 14, and 18 stand rejected under 35 U.S.C. § 103 as obvious in view of Banerjee and Tiganis.

The Examiner cites Banerjee as “teach[ing] that the angiogenic process of capillary endothelial cell proliferation is linked to the synthesis of N-linked oligosaccharide chains which is inhibited by the pyrimidine nucleoside tunicamycin” (Answer 3).¹ The Examiner cites Tiganis as “further support[ing] the recognition in the prior art of the inhibition of N-

¹ Examiner’s Answer mailed September 29, 2006.

glycosylation by tunicamycin and the disruption of vascular proliferation or angiogenesis. Tiganis teaches that the inhibition of glycoproteins by tunicamycin impairs the cell adhesion and the functional properties of the endothelial lining of the [blood] vessels” (*id.*).

From these teachings, the Examiner reasons that “if tunicamycin is a potent inhibitor of N-glycosylation and . . . this inhibition disrupts [the endothelial cell proliferation required for] . . . angiogenesis, there is clearly a reasonable expectation of success in the use of tunicamycin as an agent which would inhibit angiogenesis” (*id.*). The Examiner states that a “person of ordinary skill in the art would have been motivated to use a pyrimidine nucleoside such as tunicamycin given the prior art’s recognition of tunicamycin as an inhibitor of the pathway leading to the angiogenic process of capillary endothelial cell proliferation” (*id.* at 4). The Examiner concludes that the dosage regimen recited in the claims “is not patentable given that one of skill in the art practicing the administration of any medical compound determines the optimum dosage for each patient, based on a variety of physical and metabolic factors” (*id.*).

Appellants argue that the Examiner has “fail[ed] to establish a *prima facie* case of obviousness” (Br. 6).² Specifically, Appellants argue that Banerjee “nowhere teaches or even remotely suggests that tunicamycin could be administered to a human patient to inhibit angiogenesis” (*id.*). Appellants urge that Tiganis teaches that the administration of tunicamycin “would cause damage to brain tissue. Given this expected side effect, Tiganis . . . in no way suggests that tunicamycin be administered to a human

² Appeal Brief filed November 2, 2006.

patient. In fairness, the expectation of brain damage teaches away from the administration of tunicamycin *in vivo*” (*id.*). Appellants also urge that “[s]ince neither of the prior art references relied upon by the [E]xaminer contemplated *in vivo* administration of tunicamycin to a patient, neither reference even contemplates the further improvement of suspending then re-admi[ni]stering the treatment” (*id.* at 7).

As stated in *In re Oetiker*, 977 F.2d 1443, 1445-1446, 24 USPQ2d 1443, 1444-1445 (Fed. Cir. 1992):

[T]he examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a *prima facie* case of unpatentability. If that burden is met, the burden of coming forward with evidence or argument shifts to the applicant.

. . . .

[T]he conclusion of obviousness *vel non* is based on the preponderance of evidence and argument in the record.

We agree with Appellants that the Examiner has not established a *prima facie* case of obviousness.

The United States Supreme Court recently stated that the analysis under 35 U.S.C. § 103 “need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.” *KSR Int’l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741, 82 USPQ2d 1385, 1396 (2007). In emphasizing this flexible approach to the obviousness analysis, however, the Court also reaffirmed the principle that claims would likely be unobvious when “when the prior art teaches away” from their practice. *Id.* at 1740, 82 USPQ2d at 1395. The Court noted that it had previously held claims unobvious where the prior art warned of risks

involved in using the claimed elements. *Id.* (citing *United States v. Adams*, 383 U.S. 39, 51-52, 148 USPQ 479, 484 (1966)).

In the instant case, Tiganis discloses that “when guinea pigs and weanling rats were treated with tunicamycin the permeability of brain microvessels was increased” (Tiganis 192, citations omitted). Tiganis concludes that “the damage to brain microvessels in tunicamycin-treated animals is likely to be due to a direct action of tunicamycin on the endothelial cells” (*id.* at 199). Because Tiganis discloses that administration of tunicamycin to test animals results in damage to brain microvessels, we agree with Appellants that Tiganis teaches away from using tunicamycin as a therapeutic agent.

The Examiner argues that Tiganis does not teach away from administering tunicamycin to patients (Answer 6). Specifically, the Examiner points out that Tiganis discloses that tunicamycin was cytotoxic to dividing endothelial cells, but not confluent cells (*id.*). The Examiner also points to Tiganis’ statement that “[s]ince a feature of tunicamycin toxicity in animals is impaired permeability of brain microvessels[,] an important question is whether tunicamycin has a direct effect on microvessels *in vivo*” (*id.*, quoting Tiganis at 199, right column). The Examiner reasons that “since the prior art has recognized the levels at which tunicamycin toxicity occurs, one of skill in the art would know what dosage levels would be inappropriate” (*id.*).

We are not persuaded by this argument. We note that tunicamycin was not cytotoxic to non-dividing endothelial cells *in vitro*. We also note that Tiganis was not entirely certain as to the mechanism by which

tunicamycin damaged brain microvessels. However, Tiganis explicitly discloses that tunicamycin-treated animals suffered “damage to brain microvessels” (Tiganis 199, right column). Thus, even taking into account Tiganis’ lack of certainty regarding the precise mechanism of tunicamycin’s effects *in vivo*, Tiganis’ disclosure that the compound damages brain microvessels would, in our view, have discouraged administering it to patients.

The Examiner argues that the *in vitro* data presented in Banerjee and Tiganis is sufficient to that the claimed *in vivo* methods would have been prima facie obvious (Answer 5). The Examiner urges that “[w]hile a demonstration of *in vivo* use . . . is not absolutely required to support claims thereto, it is clear that [Appellants’] disclosure uses *in vitro* data to support the inhibition of angiogenesis while contending that the same use of *in vitro* data in the prior art is not correlative” (*id.*).

Appellants respond that “[w]hile the examiner criticizes the amount of *in vivo* data included in the specification, there are no rejections under 35 U.S.C. § 101 or 112” (Reply Br. 3).³ Appellants urge that “[t]he only issue in this application is whether the prior art fairly teaches the use of tunicamycin to treat angiogenesis in a patient as set forth in the claims” (*id.*).

We agree with Appellants that the issue before us is whether the cited references render the claimed method prima facie obvious, not whether the Specification enables the claimed method. Because Tiganis discloses that tunicamycin has adverse effects when administered *in vivo*, we conclude that one of ordinary skill would not have considered it obvious to administer the

³ Reply Brief filed November 8, 2006.

Appeal 2007-1614
Application 09/779,447

compound to inhibit angiogenesis in a patient. We therefore agree with Appellants that the Examiner has not made out a prima facie case of obviousness based on the cited references.

REVERSED

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